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Major trauma and acceleration of the ageing process

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Abstract

It is well established that numerous factors can affect the rate at which we age biologically. Diet, physical activity, lifestyle and our genes all play a major role in influencing the ageing trajectory and longevity. Major trauma affects millions globally, is the major cause of death in young adults and could influence ageing processes but has largely been ignored by biogerontologists. The long-term health consequences of physical trauma are well known in the medical community, how trauma effects the ageing process at a molecular level is not. It has long been difficult to assess ageing trajectories due to the absence of a biomarker of biological rather than chronological age. Recent advances in epigenetics have helped by identifying specific DNA methylation sites as good indicators of biological age. Recent investigations into the impact of psychological trauma and the associated physical stress on accelerating ageing as measured by epigenetic drift are promising. The physical and metabolic stress which is synonymous with physical trauma may also accelerate the ageing process. We suggest that long term epigenetic profiling is required to understand to what degree the ageing trajectory is altered by trauma, which will in turn add support for the development of novel therapies to improve health outcomes for survivors of traumatic injury.

Key Words: DNA methylation, epigenetic, ageing, trauma, injury

1. Introduction

With average life expectancy rising from the mid 40's to mid-70's within the past 250 years, the global population has never been older. This increase in lifespan is even greater within western Europe and some Asian countries where the average life expectancy is now reaching the early to mid-80s, with Japan still leading the world with a life expectancy at birth for both genders of 83.7 (WHO, 2017). Although average lifespan is increasing, the period of life spent in good health, termed healthspan, has not kept pace, with people now spending longer portions of their life in ill health (Public Health England, 2016). Understanding the factors influencing the ageing trajectory is required if we are to be better equipped to deal with the effects of demographic change. Whilst genetics and lifestyle have received much attention as influencers of the ageing trajectory (Khaw et al., 2008; Steves et al., 2012), there are other factors largely beyond our control that can have a devastating impact on health across the life course. Here we consider the potential impact of major trauma on the ageing trajectory and ageing processes.

1.1 Ageing as a malleable process

Ageing is perhaps best described as an increased inability with time to cope with biological stress resulting in increased risk of disease and death. The biological changes which occur during ageing and drive the aged phenotype have been referred to as the 'hallmarks of ageing' and were described in a landmark paper by Lopez-Otin and colleagues (Lopez-Otin et al., 2013). This paper described processes as either core drivers or downstream mediators of the ageing process. The upstream processes initiating ageing are suggested to be genomic instability, telomere attrition, loss of proteostasis and epigenetic changes and the more downstream effectors include mitochondrial dysfunction, cell senescence, loss of stem cell function and inflammation (Lopez-Otin et al., 2013). All of these increase in prevalence with age and counteracting any of these processes extends lifespan and health span in a range of species (Colman et al., 2009; Newgard and Sharpless, 2013; Tchkonja et al., 2013).

Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Aging research has experienced an unprecedented advance over recent years, particularly with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution. This review enumerates nine tentative hallmarks that represent common denominators of aging in different organisms, with special emphasis on mammalian aging. These hallmarks are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A major challenge is to dissect the interconnectedness between the candidate hallmarks and their relative contributions to aging, with the final goal of identifying pharmaceutical targets to improve human health during aging, with minimal side effects (Lopez-Otin et al., 2013).

Ageing has been shown to be a malleable process with the ageing trajectory showing a high degree of plasticity. Ageing in humans is affected in large part by lifestyle choices, disease and environmental factors. Physical activity for example is able to preserve the function of major body systems, including the musculoskeletal (Pollock et al., 2015) and immune systems into old age (Duggal et al., 2018), fasting and calorie restriction have also been shown to reduce both inflammation and the accumulation of senescent cells (Blagosklonny, 2010; Cuervo et al., 2005) and extend both life and health span in primates (Colman et al., 2009). The malleability of longevity has also been demonstrated using compounds such as rapamycin, resveratrol and metformin which target the core

ageing processes directly to extend life span in mice and other model organisms (Harrison et al., 2009; Mouchiroud et al., 2010). Conversely, various biomarkers of ageing appear to be accelerated with poor lifestyle, including increased senescent cells with obesity (Schafer et al., 2016) and raised systemic inflammation with obesity and inactivity (DeBoer, 2013).

Ageing has thus been shown to be a variable process which is affected by virtually every aspect of life. Despite this, one external factor that can have a significant impact on both lifespan and healthspan, which has so far received little attention from biogerontologists, is major trauma. Trauma, whether physical or emotional is generally described as an injury or damage to a biological organism or to the psyche of an organism as a result of a traumatic event such as blunt force trauma, burn or exposure to combat. These kinds of events can have long term impacts on health in later life as well as longevity, regardless of how well the person initially recovers from their injury.

2. Impact of major trauma on morbidity and mortality

According to the World Health Organisation, death from injury accounts for 10% of annual global deaths, equivalent to approximately 5.8 million people (WHO, 2010). Trauma disproportionately affects the young, being the leading cause of death for under 45s in the US (Lenz et al., 2007). While 5.8 million is an extremely large number of people, a much greater number are injured and survive, providing a new challenge to medicine to improve the long-term health of victims of traumatic injury.

Perhaps the most apparent long-term impact of surviving a major traumatic injury is the resulting long-term disability experienced by many patients. Evans et al, studied the prevalence of disability following trauma in a cohort of 109 young adults in the UK (90 male, aged 16-31 years) who were admitted to hospital with an injury severity score of >15. Of the 109 young adults admitted during the study 80% experienced a disability which affected their daily activities 5 years post-injury (Evans et al., 2003).

Importantly, surviving an injury may have long term health consequences that go beyond being left with a disability. Casey and Ballantyne investigated the impact of sustaining a workplace injury on the development of chronic disease (Casey and Ballantyne, 2017) using data on 251 women and 243 men in the 'Canadian community health survey' who were injured between the 2003 and 2008/9 surveys. The prevalence of chronic disease was compared between the injured and non-injured cohorts (n=4495). The study revealed that 5 years after sustaining a workplace injury the injured workers developed chronic health conditions, including migraine headaches, arthritis, hypertension, asthma, intestinal or stomach ulcers, depression/mood problems, back problems and urinary or bowel disorders at a significantly higher incidence than their matched controls. The authors conclude by stating that obtaining a workplace injury is sufficient to increase the risk of developing chronic (often age associated) diseases. This is in line with the observation that around 16 percent off all disease burden globally is the result of an injury (Krug et al., 2000).

Several retrospective analyses of linked hospital morbidity data for over 30,000 patients admitted with a burn injury between 1980 and 2012 in Western Australia by Duke and co-workers revealed increased admissions for a broad range of age-related conditions including cardiovascular disease (Duke et al., 2017), diabetes (Duke et al., 2016) and musculoskeletal conditions (Randall et al., 2015). These studies all suggest a long term impact on health after surviving a major injury.

Not only does major injury increase the risk of chronic disease, there is a growing literature providing evidence that a major traumatic injury may also have a negative impact on long term survival. Duke and colleagues also carried out two retrospective analyses of mortality rates in adults aged below and above 45 years with a burn injury using the hospital records of 6,014 patients and 25,759 matched controls. The data revealed increased mortality rate ratios of 1.4 in the over 45 years group and 1.8 in

the under 45s (Duke et al., 2015a, 2015b). It is claimed in the papers that these results are likely an underestimate of the impact of burn injury on mortality as the data included in hospital deaths. The authors suggested that the deaths occurring after discharge from hospital were potentially due to prolonged oxidative stress, hormone dysregulation and an increased risk of cancer due to the chronic hypermetabolic state often present for years following thermal injury.

In another study investigating the impact of traumatic brain injury (TBI) Brooks *et al* showed in a large-scale study (N=7228) across 20 US hospitals, that after a TBI men aged 40 or under had a 10% increase in mortality over a 20-year period compared to a control population (Brooks et al., 2013). This supports the conclusion of earlier studies which also found that long-term there is a significant increase in mortality among those who have received a TBI (Brown et al., 2004).

What these findings, and the literature more generally show is that an adverse physical injury, whether resulting in disability or not, has the potential to increase risk of disease and death, possibly due in part to an acceleration of the ageing process.

3. How might trauma impact ageing processes?

While the exact mechanisms responsible for increasing the risk of disease and mortality following trauma are yet to be fully elucidated, it is likely that there are multiple processes at work, many of which may be common between the trauma response and the ageing process. Thermal injury and many forms of trauma result in a cascade of metabolic changes which result in increased oxidative stress, inflammation, multiorgan stress, tissue loss, changes to body composition and increasing frailty (Duke et al., 2015b). These changes are often associated with ageing and the immediate response of the body to trauma includes processes that also drive ageing, including inflammation, metabolic dysregulation and epigenetic changes.

3.1 The inflammatory response to trauma

One common factor between ageing and the response to trauma is inflammation. There is a growing consensus within the literature that inflammation, as well as being a symptom of ageing, may also be one of the driving forces behind it. The chronic inflammation that develops and persists as we age has been dubbed '*inflammaging*' (Franceschi, 2008). As we age there is an increase in chronic low-grade inflammation, with raised serum levels of pro-inflammatory cytokines such as IL6, TNF α and CRP and reduced levels of anti-inflammatory cytokines such as IL10. The presence and amount of *inflammaging* is associated with increased mortality (Franceschi et al., 2007) as well as age-related frailty (Baylis et al., 2014) and disease (Chung et al., 2009; Franceschi and Campisi, 2014).

There are many factors influencing inflammaging including environmental factors such as physical inactivity (Ford, 2002), adiposity (Trayhurn and Wood, 2004), ageing of the immune system (Licastro et al., 2005) and the accumulation of senescent cells which have a pro inflammatory secretory profile (Freund et al., 2010). Any form of tissue damage that occurs during trauma will generate a sterile inflammatory response (Zhang et al., 2010; Lord et al., 2014) and in the case of some injuries such as burns this persists at a low level for many years (Jeschke et al., 2011). This increased and chronic inflammatory burden may well contribute to accelerating the ageing process.

Inflammation has been shown to increase the number of DNA lesions present within a tissue as a direct result of the increase in reactive oxygen (ROS) and nitrogen species (RNS) present during chronic inflammation (Meira et al., 2008). Trauma which often includes significant blood loss and then tissue reperfusion injury after restoration of blood volume, leads to extended ischaemia in body tissues which in turn generates ROS and RNS and leads to damage to mitochondrial DNA with long lasting

impact on mitochondrial function (Papadopoulos et al., 2013; Ruchko et al., 2005). This is one possible mechanism for accelerating the ageing process after trauma as dysregulated mitochondrial function has also been described as a hallmark of ageing (Lopez-Otin et al., 2013).

3.2 Shortened Telomeres and trauma

Telomere length is frequently used as a biomarker of ageing (Mather et al., 2011). Telomeres are hexameric repeats that aid in maintaining genomic integrity and 'cap' the ends of the chromosomes to reduce the risk of the coding portion of the genome being exposed. Due to the sequence being incompletely replicated during each cellular division, the length of a telomere is shortened with each cell divisions and can be used to establish the relative biological age of a cell. Shortened telomere length has been shown to be associated with increased risk of disease (Blackburn et al., 2015) and mortality (Cawthon et al., 2003). It is worth mentioning that while telomere length has for a long time been a standard biomarker for cellular ageing, the reliability of telomere length alone as a marker for organismal ageing is in doubt as many studies have shown an inconsistent link between telomere length and many aspects of the ageing process in humans (Sanders and Newman, 2013).

Within the literature the evidence is inconsistent regarding the impact of trauma on telomere length. Some studies have concluded that PTSD has a significant impact on telomere attrition (Kim et al., 2017), while others have reported telomere elongation in trauma victims (Boks et al., 2015). However, in two recent meta-analyses, one of which was focused on PTSD (X. Li et al., 2017) and one on the long term impact of childhood trauma (Z. Li et al., 2017), both concluded that these stressors were associated with significant telomere shortening. It is worth mentioning that there are multiple co-factors such as substance abuse which are commonly associated with childhood trauma and PTSD generally (De Bellis, 2002). These factors may also contribute to prematurely shortened telomeres making it difficult to attribute any telomere attrition purely to the presence of trauma and subsequent PTSD.

The little research that has been done on the impact of physical traumatic injury is in repeat mild traumatic brain injury models in rats, which showed telomere shortening was associated with brain injury confirmed by MRI (Wright et al., 2018). So while there is evidence to suggest that telomere shortening is present to some degree following both emotional and physical trauma, there is clearly a major research gap which needs to be filled by clinical studies.

Again it is likely that inflammation contributes to a reduction in telomere length as telomere attrition has been associated with systemic and chronic inflammation (D'Aiuto et al., 2010; Masi et al., 2011). While the exact relationship between inflammation and telomere shortening is yet to be fully understood, it is likely that they have a bi-directional influence (Kordinas et al., 2016). Damaged tissue itself has been shown to have reduced telomerase activity, decreased telomere length and increased ROS production (Felice et al., 2009). These changes are known to contribute to an inflammatory phenotype and potentially accelerate the ageing process both locally and systemically.

3.3 Cellular senescence and trauma

Cell senescence, while synonymous with ageing, is also a vital mechanism used to prevent tumorigenesis in cells which reach their replicative limit or have damaged DNA (Childs et al., 2015). Senescent cells remain metabolically active and secrete growth factors (VEGF), matrix metalloproteinases and proinflammatory cytokines, termed the Senescence Associated Secretory Phenotype (SASP) (Freund et al., 2010). Importantly animal studies have shown that deleting senescent cells extends lifespan, improves tissue quality and reduces a broad range of age-related

diseases (Naylor et al., 2013), confirming the build-up of senescent cells and the associated SASP-related inflammation as a key driver of ageing.

Senescent cells are not exclusively negative for human health, as well as being anti-oncogenic they may also have evolved for their role in wound healing. Inflammation is important for recruitment of immune cells required to prevent infection after tissue injury, but the SASP also contains factors required to limit fibrosis and scarring, notably PDGF α (Demaria et al., 2014). Fibroblasts are present at wound sites during healing to replace damaged skin and secrete the extracellular matrix found in fibrotic scar tissue. Cellular senescence is the mechanism by which excessive fibroblast proliferation is prevented (Soto-Gamez and Demaria, 2017) and mice deficient in senescent cells show compromised wound healing (Demaria et al., 2014), but the unintended consequence may well be an increased burden of senescent cells in trauma survivors, contributing to acceleration of the ageing process. Although senescent cells can be removed by immune cells such as NK cells (Sagiv and Krizhanovsky, 2013), they can induce senescence in neighbouring cells (Passos et al., 2010) thus propagating the initial generation of senescent cells if they are not removed promptly.

However, increased senescent cell burden in trauma patients has not yet been demonstrated and represents a further significant knowledge gap.

4. Measuring the age accelerating effects of trauma in its totality through epigenetics

There are a myriad of potential biomarkers for monitoring the progression of the ageing process, such as the panel of 'healthy ageing biomarkers' proposed by Lara *et al* (Lara et al., 2015), and those discussed thus far. These combinations of markers which characterise physical function, inflammatory cytokines and cellular characteristics while valid, offer a limited insight in to how well someone is ageing as a whole. Until recently there was no method of measuring complete, non-tissue dependent ageing but this problem is being overcome by the burgeoning field of epigenetics.

Epigenetics describes any modification to DNA which does not affect the DNA sequence itself. Of specific interest with regards to ageing is the epigenetic modification known as DNA methylation which is the addition of a methyl group, usually to a cytosine base. DNA methylation is also arguably the most well studied and characterised form of epigenetic modification. DNA methylation's role is to regulate gene expression. Increased methylation within the promotor region of a gene has been shown to reduce expression (Suzuki and Bird, 2008). While the exact mechanism responsible for reducing expression is yet to be fully characterised, it is currently believed that the methyl groups attached to the phosphate backbone of the DNA prevent transcription factors from successfully binding, hence preventing transcription (Medvedeva et al., 2014). Secondly it has been shown that increased levels of methylation within the gene body increases gene expression (Yang et al., 2014). Again, the exact mechanism by which this modification encourages expression is not fully understood.

The methylome gradually becomes dysregulated as we age, known as 'epigenetic drift'. This 'drift' occurs as methyl groups are erroneously added or removed which may be due to mutation, repair or failure to copy the methylation pattern during replication. As well as affecting the gene expression profile of an individual, their levels of 'epigenetic drift' can be used to accurately predict their chronological age. This epigenetic age prediction is most commonly done using the 'epigenetic clock' algorithm (Horvath, 2013). By using this highly accurate epigenetic clock ($r=0.96$) it is possible to estimate biological age, which when compared to the persons actual chronological age, reveals the rate at which ageing is occurring. We can surmise that an advanced epigenetic age represents advanced biological ageing and may also be a driving factor in the ageing process as many diseases which show accelerated epigenetic age also exhibit an ageing phenotype. These include Down's

syndrome (Horvath et al., 2015a), obesity (Horvath et al., 2014) and HIV infection (Horvath and Levine, 2015).

Interestingly, those who live into the extreme upper percentile of human life expectancy (100+ years) tend to show a decelerated rate of epigenetic ageing (Horvath et al., 2015b). It isn't yet clear if a preserved methylome is what has contributed to their longevity or is a by-product of other processes such as DNA repair being well maintained during the ageing process. A recent meta-analysis of studies of time to death predictions based on DNA methylation concluded that epigenetic regulation plays a role in longevity (Chen et al., 2016).

4.1 What we know so far about the impact of trauma on the epigenetic clock

At this time there is currently no literature describing the impact of physical trauma on epigenetic ageing as measured by the Horvath epigenetic clock algorithm. There are however a growing number of studies reporting how emotional/psychological trauma appears to be accelerating the ageing process.

The few studies in this area have focussed mainly upon PTSD. The current literature shows that just like physical trauma, psychological trauma also has a negative impact on mortality and health outcomes. Adults which have been exposed to 6 or more 'adverse childhood experiences' (ACEs) lived on average 20 years less than age-matched controls who reported no ACEs (Brown et al., 2009). This significant decrease in life expectancy may be due in part to the poorer mental health outcomes of people who experience a traumatic childhood (i.e, schizophrenia, depression, self-harm), which in turn is associated with an increased risk of behaviour based mortality (Hiroeh et al., 2001). Psychological trauma and PTSD also have an association with increased risk of disease, including classically age-related conditions such as cardiovascular disease (Dedert et al., 2010), as well as increased levels of inflammation (Baumeister et al., 2016). Recent research has now shown evidence of epigenetic age acceleration which may go some way to explaining the early onset of age associated diseases and increased risk of mortality following trauma.

One study used a cohort of 339 genotyped, non-Hispanic white military veterans with a median age of 52.5 years who had previously completed a PTSD assessment. The researchers found that while overall PTSD severity was not associated with an accelerated epigenetic age, experiencing certain symptoms, specifically 'hyperarousal' was associated with an accelerated DNA methylation age, which in turn was associated with reduced survival (E. J. Wolf et al., 2017a). In a meta-analysis of psychological trauma and its association with epigenetic age acceleration there was a small but significant increase in epigenetic age overall linked to childhood trauma and PTSD (E J. Wolf et al., 2017b). While this meta-analysis does not offer a mechanistic insight into what is driving the ageing process forward, it does lend credence to the proposal that biological stress may accelerate the ageing process.

What the literature has undoubtedly shown is that ageing, disease and biological stress are inexorably linked. It has been established that both biological stress, whether inflammation or adverse conditions and diseases, are linked in some way to accelerated ageing.

5. Trauma and ageing, commonalities and differences

While it may be the case that both ageing and trauma share multiple pathogenic mechanisms, as outlined in Table 1 there are also some notable differences that largely relate to the scale and kinetic of the disturbance. For example, the extensive tissue damage and risk of multiple organ dysfunction (Durham et al., 2003) associated with a physical traumatic injury are not seen in physiological ageing

though there is a gradual decline in many body systems resulting in multimorbidity (Ryan et al., 2015). Functional decline is thus a feature of both and a specific shared characteristic is sarcopenia, which is driven by several factors including physical inactivity and inflammation (Bano et al., 2017; Parry and Puthucherry, 2015).

In relation to inflammation, another feature of trauma and ageing, the level and chronicity of this increase in is drastically different. In trauma systemic inflammation is very high and at a level similar to a major infection (Lu et al., 2009; Namas et al., 2009) and the onset is sudden, whereas the inflammation associated with the ageing process is at a low level, only 2-4 fold that seen in young adults, and is chronic persisting potentially for decades (Bartlett et al., 2012; Franceschi et al., 2007). It is worth mentioning however that low level chronic inflammation does occur following some injuries such as burns, here chronic low grade inflammation can persist for years in a similar way to the chronic inflammation we classically associate with ageing (Jeschke et al., 2011).

The accumulation of senescent cells, something classically associated with ageing, also occurs following trauma, although similar to inflammation the scale and timeframe of this accumulation differs. Following trauma, there is an increase in the presence of senescent cells near the injury site, which aids in tissue repair (Deursen, 2014), with ageing the increasing number of senescent cells is not tissue specific and occurs globally at a gradual rate (Burton, 2009).

Here, we posit not that both age and trauma related physiological changes are identical, rather that they share some common mechanisms and their magnitude and kinetics differ but achieve the same end – a predisposition to an aged phenotype. Furthermore it bears mentioning some of the gaps in our understanding of the relationship between trauma and ageing and limitations in the existing data. Ideally there would be multiple studies within the literature examining the effect of trauma on multiple biomarkers of ageing (Horvath, 2013; Lara et al., 2015) in healthy adults of all ages with no confounding comorbidities or health behaviours. Due to the nature of trauma research, this is not the case. Many of the cohorts who feature in the studies described are heterogeneous, of differing ethnicity, injury severity, BMI and comorbidities. Many of the people enrolled into trauma research studies may already be showing many of the symptoms we associate with ageing prior to their injury, particularly the frail older patient whose injury may well be the result of a fall. In the case of the younger patient their injury may be the result of, or lead to, risky lifestyle behaviours such as substance abuse. Therefore more clinical work is needed to assess the influence these cofactors have on the relationship between trauma and ageing.

6. Conclusions and future directions

Outlined throughout this review are the long-term health consequences of major trauma for survivors of both physical and psychological trauma, including shortened lifespan and increased risk of early onset of age-related diseases. At the clinical level this would support our contention that trauma accelerates the ageing process and certainly processes known to drive the ageing phenotype, such as chronic systemic inflammation, compromised mitochondrial function do appear to be increased after trauma. However further research is required to test this concept at the cellular and molecular level with reliable and quantitative biomarkers of biological ageing. Here an analysis of DNA methylation for specific genomic regions associated with ageing to give 'a biological age' versus chronological age following trauma holds promise, but the studies in PTSD need to be extended and research in to physical trauma and DNA methylation are required. In addition, the use of a broad panel of more conventional blood-based biomarkers of ageing such as those outlined by Lara et al, would also be informative (Lara et al., 2015).

The benefit of knowing if ageing is accelerated after trauma is not merely to expand our understanding of the consequences of trauma. The field of biogerontology has now advanced to such a stage that anti-ageing therapeutics are now in clinical trials to delay the onset or progress of age-related diseases. Many of these are repurposed drugs such as metformin, which affect core ageing processes and are able to delay ageing in a variety of species (Podhorecka et al., 2017), or drugs that target senescent cells, termed senolytics (Kirkland et al., 2017). In this way we may be able to improve long term outcomes for survivors of major trauma.

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Table 1

| Characteristic | Presence in Trauma | Presence in Ageing | Shared Characteristic |
|-------------------------------------|---|---|---|
| Inflammation | Acute, high level inflammation (Lu et al., 2009; Namas et al., 2009) | Chronic low level inflammation (Franceschi, 2008) | Chronic inflammation in burn injury (Jeschke et al., 2008) |
| Functional decline in organ systems | Multiple organ dysfunction (Durham et al., 2003) | Gradual decline in many body systems over time; multimorbidity (Ryan et al., 2015) | Reduced lean body mass, (Bano et al., 2017; Morley et al., 2010; Parry and Puthuchear, 2015) fatigue; disability (Evans et al., 2003; WHO, 2011) |
| Immune compromise | Acute immunoparesis and increased susceptibility to infection and sepsis (Hietbrink et al., 2006) | Immune remodelling with broad compromise to immunity (Dorshkind et al., 2009) | Reduced neutrophil function (Butcher et al., 2001; Hampson et al., 2017); increased risk of infection |
| DNA alterations | Acute and large scale genomic change (Xiao et al., 2011) | Genome instability (Moskalev et al., 2013) | Epigenetic alterations after psychological trauma (E J. Wolf et al., 2017b) and with age (Horvath, 2013); Telomere attrition (Jiang et al., 2007; X. Li et al., 2017; Z. Li et al., 2017) |
| Metabolic disturbance | Acute Increase in catabolism (Jeschke et al., 2008) | Insulin resistance due to changes in body composition (Karakelides et al., 2010), anabolic resistance (Roubenoff, 2003) | Long term metabolic disturbance after burn – catabolism (Hart et al., 2000), insulin resistance (Williams et al., 2009) |
| Cell senescence | Acute Senescence (Deursen, 2014) | Increase in cell senescence over time (Velarde and Demaria, 2016) | Senescent cells primarily at wound site (Campisi, 2005; Deursen, 2014) |

Table 1: Features present in trauma and ageing and the characteristics they share.

References

- Bano, G., Trevisan, C., Carraro, S., Solmi, M., Luchini, C., Stubbs, B., Manzato, E., Sergi, G., Veronese, N., 2017. Inflammation and sarcopenia: A systematic review and meta-analysis. *Maturitas* 96, 10–15. <https://doi.org/10.1016/j.maturitas.2016.11.006>
- Bartlett, D.B., Firth, C.M., Phillips, A.C., Moss, P., Baylis, D., Syddall, H., Sayer, A.A., Cooper, C., Lord, J.M., 2012. The age-related increase in low-grade systemic inflammation (Inflammaging) is not driven by cytomegalovirus infection. *Aging Cell* 11, 912–915. <https://doi.org/10.1111/j.1474-9726.2012.00849.x> [doi]
- Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Mol. Psychiatry* 21, 642–649. <https://doi.org/10.1038/mp.2015.67>
- Baylis, D., Ntani, G., Edwards, M.H., Syddall, H.E., Bartlett, D.B., Dennison, E.M., Martin-Ruiz, C., Zglinicki, T. von, Kuh, D., Lord, J.M., Sayer, A.A., Cooper, C., 2014. Inflammation, telomere length, and grip strength: a 10-year longitudinal study. *Calcif. Tissue Int.* 95, 54–63. <https://doi.org/10.1007/s00223-014-9862-7> [doi]
- Blackburn, E.H., Epel, E.S., Lin, J., 2015. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science* 350, 1193–1198. <https://doi.org/10.1126/science.aab3389>
- Blagosklonny, M.V., 2010. Calorie restriction: Decelerating mTOR-driven aging from cells to organisms (including humans). *Cell Cycle* 9, 683–688. <https://doi.org/10.4161/cc.9.4.10766>
- Boks, M.P., Mierlo, H.C. van, Rutten, B.P.F., Radstake, T.R.D.J., Witte, L.D., Geuze, E., Horvath, S., Schalkwyk, L.C., Vinkers, C.H., Broen, J.C.A., Vermetten, E., 2015. Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. <https://doi.org/10.1016/j.psyneuen.2014.07.011>
- Brooks, J.C., Strauss, D.J., Shavelle, R.M., Paculdo, D.R., Hammond, F.M., Harrison-Felix, C.L., 2013. Long-term disability and survival in traumatic brain injury: results from the National Institute on Disability and Rehabilitation Research Model Systems. *Arch. Phys. Med. Rehabil.* 94, 2203–2209. <https://doi.org/10.1016/j.apmr.2013.07.005> [doi]
- Brown, A.W., Leibson, C.L., Malec, J.F., Perkins, P.K., Diehl, N.N., Larson, D.R., 2004. Long-term survival after traumatic brain injury: a population-based analysis. *NeuroRehabilitation* 19, 37–43.
- Brown, D.W., Anda, R.F., Tiemeier, H., Felitti, V.J., Edwards, V.J., Croft, J.B., Giles, W.H., 2009. Adverse childhood experiences and the risk of premature mortality. *Am. J. Prev. Med.* 37, 389–396.
- Burton, D.G.A., 2009. Cellular senescence, ageing and disease. *AGE* 31, 1–9. <https://doi.org/10.1007/s11357-008-9075-y>
- Butcher, S.K., Chahal, H., Nayak, L., Sinclair, A., Henriquez, N.V., Sapey, E., O'Mahony, D., Lord, J.M., 2001. Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. *J. Leukoc. Biol.* 70, 881–886.
- Campisi, J., 2005. Senescent Cells, Tumor Suppression, and Organismal Aging: Good Citizens, Bad Neighbors. <https://doi.org/10.1016/j.cell.2005.02.003>
- Casey, R., Ballantyne, P.J., 2017. Diagnosed Chronic Health Conditions Among Injured Workers With Permanent Impairments and the General Population. *J. Occup. Environ. Med.* 59, 486–496. <https://doi.org/10.1097/JOM.0000000000000998> [doi]
- Cawthon, R.M., Smith, K.R., O'Brien, E., Sivatchenko, A., Kerber, R.A., 2003. Association between telomere length in blood and mortality in people aged 60 years or older. *The Lancet* 361, 393–395. [https://doi.org/10.1016/S0140-6736\(03\)12384-7](https://doi.org/10.1016/S0140-6736(03)12384-7)

- Chen, B.H., Marioni, R.E., Colicino, E., Peters, M.J., Ward-Caviness, C.K., Tsai, P.-C., Roetker, N.S., Just, A.C., Demerath, E.W., Guan, W., Bressler, J., Fornage, M., Studenski, S., Vandiver, A.R., Moore, A.Z., Tanaka, T., Kiel, D.P., Liang, L., Vokonas, P., Schwartz, J., Lunetta, K.L., Murabito, J.M., Bandinelli, S., Hernandez, D.G., Melzer, D., Nalls, M., Pilling, L.C., Price, T.R., Singleton, A.B., Gieger, C., Holle, R., Kretschmer, A., Kronenberg, F., Kunze, S., Linseisen, J., Meisinger, C., Rathmann, W., Waldenberger, M., Visscher, P.M., Shah, S., Wray, N.R., McRae, A.F., Franco, O.H., Hofman, A., Uitterlinden, A.G., Absher, D., Assimes, T., Levine, M.E., Lu, A.T., Tsao, P.S., Hou, L., Manson, J.E., Carty, C.L., LaCroix, A.Z., Reiner, A.P., Spector, T.D., Feinberg, A.P., Levy, D., Baccarelli, A., van Meurs, J., Bell, J.T., Peters, A., Deary, I.J., Pankow, J.S., Ferrucci, L., Horvath, S., 2016. DNA methylation-based measures of biological age: meta-analysis predicting time to death. *Aging* 8, 1844–1865.
<https://doi.org/10.18632/aging.101020>
- Childs, B.G., Durik, M., Baker, D.J., Deursen, J.M. van, 2015. Cellular senescence in aging and age-related disease: from mechanisms to therapy. *Nat. Med.* 21, 1424–1435.
<https://doi.org/10.1038/nm.4000> [doi]
- Chung, H.Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A.Y., Carter, C., Yu, B.P., Leeuwenburgh, C., 2009. Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Res. Rev.* 8, 18–30.
- Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T.M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., Weindruch, R., 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 325, 201–204.
<https://doi.org/10.1126/science.1173635>
- Cuervo, A.M., Bergamini, E., Brunk, U.T., Dröge, W., Ffrench, M., Terman, A., 2005. Autophagy and Aging: The Importance of Maintaining “Clean” Cells. *Autophagy* 1, 131–140.
<https://doi.org/10.4161/auto.1.3.2017>
- D’Aiuto, F., Nibali, L., Parkar, M., Patel, K., Suvan, J., Donos, N., 2010. Oxidative stress, systemic inflammation, and severe periodontitis. *J. Dent. Res.* 89, 1241–1246.
<https://doi.org/10.1177/0022034510375830> [doi]
- De Bellis, M.D., 2002. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* 27, 155–170.
[https://doi.org/10.1016/S0306-4530\(01\)00042-7](https://doi.org/10.1016/S0306-4530(01)00042-7)
- DeBoer, M.D., 2013. Obesity, systemic inflammation, and increased risk for cardiovascular disease and diabetes among adolescents: a need for screening tools to target interventions. *Nutr. Burbank Los Angel. Cty. Calif* 29, 379–386. <https://doi.org/10.1016/j.nut.2012.07.003>
- Dedert, E.A., Calhoun, P.S., Watkins, L.L., Sherwood, A., Beckham, J.C., 2010. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. *Ann. Behav. Med. Publ. Soc. Behav. Med.* 39, 61–78. <https://doi.org/10.1007/s12160-010-9165-9> [doi]
- Demaria, M., Ohtani, N., Youssef, S.A., Rodier, F., Toussaint, W., Mitchell, J.R., Laberge, R.M., Vijg, J., Steeg, H.V., Dolle, M.E., Hoeijmakers, J.H., Bruin, A. de, Hara, E., Campisi, J., 2014. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Dev. Cell* 31, 722–733. <https://doi.org/10.1016/j.devcel.2014.11.012> [doi]
- Deursen, J.M. van, 2014. The role of senescent cells in ageing. *Nature* 509, 439–446.
<https://doi.org/10.1038/nature13193>
- Dorshkind, K., Montecino-Rodriguez, E., Signer, R.A.J., 2009. The ageing immune system: is it ever too old to become young again? *Nat. Rev. Immunol.* 9, 57–62.
<https://doi.org/10.1038/nri2471>
- Duggal, N.A., Pollock, R.D., Lazarus, N.R., Harridge, S., Lord, J.M., 2018. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell* 17. <https://doi.org/10.1111/accel.12750>

- Duke, J.M., Boyd, J.H., Rea, S., Randall, S.M., Wood, F.M., 2015a. Long-term mortality among older adults with burn injury: a population-based study in Australia. *Bull. World Health Organ.* 93, 400–406. <https://doi.org/10.2471/BLT.14.149146> [doi]
- Duke, J.M., Randall, S.M., Fear, M.W., Boyd, J.H., O'Halloran, E., Rea, S., Wood, F.M., 2016. Increased admissions for diabetes mellitus after burn. *Burns* 42, 1734–1739. <https://doi.org/10.1016/j.burns.2016.06.005>
- Duke, J.M., Randall, S.M., Fear, M.W., O'Halloran, E., Boyd, J.H., Rea, S., Wood, F.M., 2017. Long term cardiovascular impacts after burn and non-burn trauma: A comparative population-based study. *Burns* 43, 1662–1672. <https://doi.org/10.1016/j.burns.2017.08.001>
- Duke, J.M., Rea, S., Boyd, J.H., Randall, S.M., Wood, F.M., 2015b. Mortality After Burn Injury in Children: A 33-year Population-Based Study. *PEDIATRICS* 135, e903–e910. <https://doi.org/10.1542/peds.2014-3140>
- Durham, R.M., Moran, J.J., Mazuski, J.E., Shapiro, M.J., Baue, A.E., Flint, L.M., 2003. Multiple Organ Failure in Trauma Patients. *J. Trauma Acute Care Surg.* 55, 608. <https://doi.org/10.1097/01.TA.0000092378.10660.D1>
- Evans, S.A., Airey, M.C., Chell, S.M., Connelly, J.B., Rigby, A.S., Tennant, A., 2003. Disability in young adults following major trauma: 5 year follow up of survivors. *BMC Public Health* 3, 8.
- Felice, B.D., Wilson, R.R., Nacca, M., 2009. Telomere shortening may be associated with human keloids. *BMC Med. Genet.* 10, 110. <https://doi.org/10.1186/1471-2350-10-110> [doi]
- Ford, E.S., 2002. Does exercise reduce inflammation? Physical activity and C-reactive protein among US adults. *Epidemiology* 13, 561–568.
- Franceschi, C., 2008. Inflammaging as a Major Characteristic of Old People: Can It Be Prevented or Cured? *Nutr. Rev.* 65, S173–S176. <https://doi.org/10.1111/j.1753-4887.2007.tb00358.x>
- Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J. Gerontol. Biol. Sci. Med. Sci.* 69 Suppl 1, 4. <https://doi.org/10.1093/gerona/glu057> [doi]
- Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., Panourgia, M.P., Invidia, L., Celani, L., Scurti, M., Cevenini, E., Castellani, G.C., Salvioli, S., 2007. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech. Ageing Dev.* 128, 92–105. [https://doi.org/S0047-6374\(06\)00249-1](https://doi.org/S0047-6374(06)00249-1) [pii]
- Freund, A., Orjalo, A.V., Desprez, P.Y., Campisi, J., 2010. Inflammatory networks during cellular senescence: causes and consequences. *Trends Mol. Med.* 16, 238–246. <https://doi.org/10.1016/j.molmed.2010.03.003> [doi]
- Hampson, P., Dinsdale, R.J., Wearn, C.M., Bamford, A.L., Bishop, J.R.B., Hazeldine, J., Moiemmen, N.S., Harrison, P., Lord, J.M., 2017. Neutrophil Dysfunction, Immature Granulocytes, and Cell-free DNA are Early Biomarkers of Sepsis in Burn-injured Patients: A Prospective Observational Cohort Study. *Ann. Surg.* 265, 1241–1249. <https://doi.org/10.1097/SLA.0000000000001807>
- Harrison, D.E., Strong, R., Sharp, Z.D., Nelson, J.F., Astle, C.M., Flurkey, K., Nadon, N.L., Wilkinson, J.E., Frenkel, K., Carter, C.S., Pahor, M., Javors, M.A., Fernandez, E., Miller, R.A., 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392–395. <https://doi.org/10.1038/nature08221>
- Hart, D.W., Wolf, S.E., Mlcak, R., Chinkes, D.L., Ramzy, P.I., Obeng, M.K., Ferrando, A.A., Wolfe, R.R., Herndon, D.N., 2000. Persistence of muscle catabolism after severe burn. *Surgery* 128, 312–319. <https://doi.org/10.1067/msy.2000.108059>
- Hietbrink, F., Koenderman, L., Rijkers, G., Leenen, L., 2006. Trauma: the role of the innate immune system. *World J. Emerg. Surg.* 1, 15. <https://doi.org/10.1186/1749-7922-1-15>
- Hiroeh, U., Appleby, L., Mortensen, P.B., Dunn, G., 2001. Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. [https://doi.org/10.1016/S0140-6736\(01\)07216-6](https://doi.org/10.1016/S0140-6736(01)07216-6)
- Horvath, S., 2013. DNA methylation age of human tissues and cell types. *Genome Biol.* 14, R115. <https://doi.org/gb-2013-14-10-r115> [pii]

- Horvath, S., Erhart, W., Brosch, M., Ammerpohl, O., von Schönfels, W., Ahrens, M., Heits, N., Bell, J.T., Tsai, P.-C., Spector, T.D., Deloukas, P., Siebert, R., Sipos, B., Becker, T., Röcken, C., Schafmayer, C., Hampe, J., 2014. Obesity accelerates epigenetic aging of human liver. *Proc. Natl. Acad. Sci. U. S. A.* 111, 15538–15543. <https://doi.org/10.1073/pnas.1412759111>
- Horvath, S., Garagnani, P., Bacalini, M.G., Pirazzini, C., Salvioli, S., Gentilini, D., Di Blasio, A.M., Giuliani, C., Tung, S., Vinters, H.V., Franceschi, C., 2015a. Accelerated epigenetic aging in Down syndrome. *Aging Cell* 14, 491–495. <https://doi.org/10.1111/ace.12325>
- Horvath, S., Levine, A.J., 2015. HIV-1 Infection Accelerates Age According to the Epigenetic Clock. *J. Infect. Dis.* 212, 1563–1573. <https://doi.org/10.1093/infdis/jiv277>
- Horvath, S., Pirazzini, C., Bacalini, M.G., Gentilini, D., Di Blasio, A.M., Delledonne, M., Mari, D., Arosio, B., Monti, D., Passarino, G., De Rango, F., D'Aquila, P., Giuliani, C., Marasco, E., Collino, S., Descombes, P., Garagnani, P., Franceschi, C., 2015b. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. *Aging* 7, 1159–1170.
- Jeschke, M.G., Chinkes, D.L., Finnerty, C.C., Kulp, G., Suman, O.E., Norbury, W.B., Branski, L.K., Gauglitz, G.G., Mlcak, R.P., Herndon, D.N., 2008. Pathophysiologic response to severe burn injury. *Ann. Surg.* 248, 387–401. <https://doi.org/10.1097/SLA.0b013e3181856241> [doi]
- Jeschke, M.G., Gauglitz, G.G., Kulp, G.A., Finnerty, C.C., Williams, F.N., Kraft, R., Suman, O.E., Mlcak, R.P., Herndon, D.N., 2011. Long-Term Persistence of the Pathophysiologic Response to Severe Burn Injury. *PLoS ONE* 6, e21245. <https://doi.org/10.1371/journal.pone.0021245>
- Jiang, H., Ju, Z., Rudolph, K.L., 2007. Telomere shortening and ageing. *Z. Gerontol. Geriatr.* 40, 314–324. <https://doi.org/10.1007/s00391-007-0480-0> [doi]
- Karakelides, H., Irving, B.A., Short, K.R., O'Brien, P., Nair, K.S., 2010. Age, Obesity, and Sex Effects on Insulin Sensitivity and Skeletal Muscle Mitochondrial Function. *Diabetes* 59, 89–97. <https://doi.org/10.2337/db09-0591>
- Khaw, K.-T., Wareham, N., Bingham, S., Welch, A., Luben, R., Day, N., 2008. Combined Impact of Health Behaviours and Mortality in Men and Women: The EPIC-Norfolk Prospective Population Study. *PLoS Med.* 5, 9.
- Kim, T.Y., Kim, S.J., Choi, J.R., Lee, S.T., Kim, J., Hwang, I.S., Chung, H.G., Choi, J.H., Kim, H.W., Kim, S.H., Kang, J.I., 2017. The effect of trauma and PTSD on telomere length: An exploratory study in people exposed to combat trauma. *Sci. Rep.* 7, w. <https://doi.org/10.1038/s41598-017-04682-w> [doi]
- Kirkland, J.L., Tchkonja, T., Zhu, Y., Niedernhofer, L.J., Robbins, P.D., 2017. The Clinical Potential of Senolytic Drugs. *J. Am. Geriatr. Soc.* 65, 2297–2301. <https://doi.org/10.1111/jgs.14969>
- Kordinas, V., Ioannidis, A., Chatzipanagiotou, S., 2016. The Telomere/Telomerase System in Chronic Inflammatory Diseases. Cause or Effect? *Genes* 7, 10.3390/genes7090060. <https://doi.org/10.3390/genes7090060> [doi]
- Krug, E.G., Sharma, G.K., Lozano, R., 2000. The global burden of injuries. *Am. J. Public Health* 90, 523–526.
- Lara, J., Cooper, R., Nissan, J., Ginty, A.T., Khaw, K.-T., Deary, I.J., Lord, J.M., Kuh, D., Mathers, J.C., 2015. A proposed panel of biomarkers of healthy ageing. *BMC Med.* 13, 222.
- Lenz, A., Franklin, G.A., Cheadle, W.G., 2007. Systemic inflammation after trauma. *Injury* 38, 1336–1345. [https://doi.org/S0020-1383\(07\)00418-4](https://doi.org/S0020-1383(07)00418-4) [pii]
- Li, X., Wang, J., Zhou, J., Huang, P., Li, J., 2017. The association between post-traumatic stress disorder and shorter telomere length: A systematic review and meta-analysis. *J. Affect. Disord.* 218, 322–326. <https://doi.org/10.1016/j.jad.2017.03.048>
- Li, Z., He, Y., Wang, D., Tang, J., Chen, X., 2017. Association between childhood trauma and accelerated telomere erosion in adulthood: A meta-analytic study. *J. Psychiatr. Res.* 93, 64–71. <https://doi.org/10.1016/j.jpsychires.2017.06.002>
- Licastro, F., Candore, G., Lio, D., Porcellini, E., Colonna-Romano, G., Franceschi, C., Caruso, C., 2005. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. *Immun. Ageing* 2, 8.

- Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. *Cell* 153, 1194–1217. <https://doi.org/10.1016/j.cell.2013.05.039> [doi]
- Lord, J.M., Midwinter, M.J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E.J., Koenderman, L., Kubes, P., Lilford, R.J., 2014. The systemic immune response to trauma: an overview of pathophysiology and treatment. *The Lancet* 384, 1455–1465.
- Lu, J., Goh, S.J., Tng, P.Y.L., Deng, Y.Y., Ling, E.-A., Moochhala, S., 2009. Systemic inflammatory response following acute traumatic brain injury. *Front. Biosci. Landmark Ed.* 14, 3795–3813.
- Masi, S., Salpea, K.D., Li, K., Parkar, M., Nibali, L., Donos, N., Patel, K., Taddei, S., Deanfield, J.E., D’Aiuto, F., Humphries, S.E., 2011. Oxidative stress, chronic inflammation, and telomere length in patients with periodontitis. <https://doi.org/10.1016/j.freeradbiomed.2010.12.031>
- Mather, K.A., Jorm, A.F., Parslow, R.A., Christensen, H., 2011. Is Telomere Length a Biomarker of Aging? A Review. *J. Gerontol. Ser. A* 66A, 202–213. <https://doi.org/10.1093/gerona/glq180>
- Medvedeva, Y.A., Khamis, A.M., Kulakovskiy, I.V., Ba-Alawi, W., Bhuyan, M.S.I., Kawaji, H., Lassmann, T., Harbers, M., Forrest, A.R., Bajic, V.B., 2014. Effects of cytosine methylation on transcription factor binding sites. *BMC Genomics* 15, 119. <https://doi.org/10.1186/1471-2164-15-119>
- Meira, L.B., Bugni, J.M., Green, S.L., Lee, C.W., Pang, B., Borenshtein, D., Rickman, B.H., Rogers, A.B., Moroski-Erkul, C.A., McFaline, J.L., Schauer, D.B., Dedon, P.C., Fox, J.G., Samson, L.D., 2008. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J. Clin. Invest.* 118, 2516–2525. <https://doi.org/10.1172/JCI35073> [doi]
- Morley, J.E., Argiles, J.M., Evans, W.J., Bhasin, S., Cella, D., Deutz, N.E.P., Doehner, W., Fearon, K.C.H., Ferrucci, L., Hellerstein, M.K., Kalantar-Zadeh, K., Lochs, H., MacDonald, N., Mulligan, K., Muscaritoli, M., Ponikowski, P., Posthauer, M.E., Fanelli, F.R., Schambelan, M., Schols, A.M.W.J., Schuster, M.W., Anker, S.D., 2010. Nutritional Recommendations for the Management of Sarcopenia. *J. Am. Med. Dir. Assoc.* 11, 391–396. <https://doi.org/10.1016/j.jamda.2010.04.014>
- Moskalev, A.A., Shaposhnikov, M.V., Plyusnina, E.N., Zhavoronkov, A., Budovsky, A., Yanai, H., Fraifeld, V.E., 2013. The role of DNA damage and repair in aging through the prism of Koch-like criteria. *Ageing Res. Rev.* 12, 661–684. <https://doi.org/10.1016/j.arr.2012.02.001>
- Mouchiroud, L., Molin, L., Dalli  re, N., Solari, F., 2010. Life span extension by resveratrol, rapamycin, and metformin: The promise of dietary restriction mimetics for an healthy aging. *Biofactors* 36, 377–382.
- Namas, R., Ghuma, A., Hermus, L., Zamora, R., Okonkwo, D., Billiar, T., Vodovotz, Y., 2009. The Acute Inflammatory Response in Trauma / Hemorrhage and Traumatic Brain Injury: Current State and Emerging Prospects. *Libyan J. Med.* 4, 136–148. <https://doi.org/10.4176/090325>
- Naylor, R.M., Baker, D.J., Deursen, J.M. van, 2013. Senescent cells: a novel therapeutic target for aging and age-related diseases. *Clin. Pharmacol. Ther.* 93, 105–116. <https://doi.org/10.1038/clpt.2012.193> [doi]
- Newgard, C.B., Sharpless, N.E., 2013. Coming of age: molecular drivers of aging and therapeutic opportunities. *J. Clin. Invest.* 123, 946–950. <https://doi.org/10.1172/JCI68833>
- Papadopoulos, D., Siempis, T., Theodorakou, E., Tsoulfas, G., 2013. Hepatic Ischemia and Reperfusion Injury and Trauma: Current Concepts. *Arch. Trauma Res.* 2, 63–70. <https://doi.org/10.5812/at.12501>
- Parry, S.M., Puthuchear, Z.A., 2015. The impact of extended bed rest on the musculoskeletal system in the critical care environment. *Extreme Physiol. Med.* 4. <https://doi.org/10.1186/s13728-015-0036-7>
- Passos, J.F., Nelson, G., Wang, C., Richter, T., Simillion, C., Proctor, C.J., Miwa, S., Olijslagers, S., Hallinan, J., Wipat, A., Saretzki, G., Rudolph, K.L., Kirkwood, T.B., Zglinicki, T. von, 2010. Feedback between p21 and reactive oxygen production is necessary for cell senescence. *Mol. Syst. Biol.* 6, 347. <https://doi.org/10.1038/msb.2010.5> [doi]

- Podhorecka, M., Ibanez, B., Dmoszyńska, A., 2017. Metformin - its potential anti-cancer and anti-aging effects. *Postepy Hig. Med. Doswiadczalnej Online* 71, 170–175.
- Pollock, R.D., Carter, S., Velloso, C.P., Duggal, N.A., Lord, J.M., Lazarus, N.R., Harridge, S.D.R., 2015. An investigation into the relationship between age and physiological function in highly active older adults. *J. Physiol.* 593, 657–680. <https://doi.org/10.1113/jphysiol.2014.282863>
- Public Health England, 2016. Chapter 1: life expectancy and healthy life expectancy [WWW Document]. GOV.UK. URL <https://www.gov.uk/government/publications/health-profile-for-england/chapter-1-life-expectancy-and-healthy-life-expectancy> (accessed 4.23.18).
- Randall, S.M., Fear, M.W., Wood, F.M., Rea, S., Boyd, J.H., Duke, J.M., 2015. Long-term musculoskeletal morbidity after adult burn injury: a population-based cohort study. *BMJ Open* 5, e009395. <https://doi.org/10.1136/bmjopen-2015-009395>
- Roubenoff, R., 2003. Catabolism of aging: is it an inflammatory process? *Curr. Opin. Clin. Nutr. Metab. Care* 6, 295–299. <https://doi.org/10.1097/01.mco.0000068965.34812.62>
- Ruchko, M., Gorodnya, O., LeDoux, S.P., Alexeyev, M.F., Al-Mehdi, A.-B., Gillespie, M.N., 2005. Mitochondrial DNA damage triggers mitochondrial dysfunction and apoptosis in oxidant-challenged lung endothelial cells. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* 288, L530–L535. <https://doi.org/10.1152/ajplung.00255.2004>
- Ryan, A., Wallace, E., O'Hara, P., Smith, S.M., 2015. Multimorbidity and functional decline in community-dwelling adults: a systematic review. *Health Qual. Life Outcomes* 13. <https://doi.org/10.1186/s12955-015-0355-9>
- Sagiv, A., Krizhanovsky, V., 2013. Immunosurveillance of senescent cells: the bright side of the senescence program. *Biogerontology* 14, 617–628.
- Sanders, J.L., Newman, A.B., 2013. Telomere Length in Epidemiology: A Biomarker of Aging, Age-Related Disease, Both, or Neither? *Epidemiol. Rev.* 35, 112–131. <https://doi.org/10.1093/epirev/mxs008>
- Schafer, M.J., White, T.A., Evans, G., Tonne, J.M., Verzosa, G.C., Stout, M.B., Mazula, D.L., Palmer, A.K., Baker, D.J., Jensen, M.D., Torbenson, M.S., Miller, J.D., Ikeda, Y., Tchkonja, T., Deursen, J.M. van, Kirkland, J.L., LeBrasseur, N.K., 2016. Exercise Prevents Diet-induced Cellular Senescence in Adipose Tissue. *Diabetes* db15029. <https://doi.org/10.2337/db15-0291>
- Soto-Gamez, A., Demaria, M., 2017. Therapeutic interventions for aging: the case of cellular senescence. *Drug Discov. Today* 22, 786–795. [https://doi.org/S1359-6446\(17\)30017-X](https://doi.org/S1359-6446(17)30017-X) [pii]
- Steves, C.J., Spector, T.D., Jackson, S.H.D., 2012. Ageing, genes, environment and epigenetics: what twin studies tell us now, and in the future. *Age Ageing* 41, 581–586. <https://doi.org/10.1093/ageing/afs097>
- Suzuki, M.M., Bird, A., 2008. DNA methylation landscapes: provocative insights from epigenomics. *Nat. Rev. Genet.* 9, 465–476. <https://doi.org/10.1038/nrg2341>
- Tchkonja, T., Zhu, Y., van Deursen, J., Campisi, J., Kirkland, J.L., 2013. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J. Clin. Invest.* 123, 966–972. <https://doi.org/10.1172/JCI64098>
- Trayhurn, P., Wood, I.S., 2004. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br. J. Nutr.* 92, 347–355. <https://doi.org/10.1079/BJN20041213>
- Velarde, M.C., Demaria, M., 2016. Targeting Senescent Cells: Possible Implications for Delaying Skin Aging: A Mini-Review. *Gerontology* 62, 513–518. <https://doi.org/10.1159/000444877>
- WHO, 2017. WHO health statistics 2017: monitoring health for the SDGs.
- WHO, 2011. World Report on Disability 350.
- WHO, 2010. Injuries and violence, the facts. (World Health Organisation).
- Williams, F.N., Herndon, D.N., Jeschke, M.G., 2009. The hypermetabolic response to burn injury and interventions to modify this response. *Clin. Plast. Surg.* 36, 583–596. <https://doi.org/10.1016/j.cps.2009.05.001> [doi]

- Wolf, E. J., Logue, M.W., Stoop, T.B., Schichman, S.A., Stone, A., Sadeh, N., Hayes, J.P., Miller, M.W., 2017a. Accelerated DNA Methylation Age: Associations with PTSD and Mortality. *Psychosom. Med.* <https://doi.org/10.1097/PSY.0000000000000506> [doi]
- Wolf, E.J., Maniates, H., Nugent, N., Maihofer, A.X., Armstrong, D., Ratanatharathorn, A., Ashley-Koch, A.E., Garrett, M., Kimbrel, N.A., Lori, A., 2017b. Traumatic Stress and Accelerated DNA Methylation Age: A Meta-Analysis. *Psychoneuroendocrinology*.
- Wright, D.K., O'Brien, T.J., Mychasiuk, R., Shultz, S.R., 2018. Telomere length and advanced diffusion MRI as biomarkers for repetitive mild traumatic brain injury in adolescent rats. *NeuroImage Clin.* 18, 315–324. <https://doi.org/10.1016/j.nicl.2018.01.033>
- Xiao, W., Mindrinos, M.N., Seok, J., Cuschieri, J., Cuenca, A.G., Gao, H., Hayden, D.L., Hennessy, L., Moore, E.E., Minei, J.P., 2011. A genomic storm in critically injured humans. *J. Exp. Med.* 208, 2581–2590.
- Yang, X., Han, H., De Carvalho, D.D., Lay, F.D., Jones, P.A., Liang, G., 2014. Gene Body Methylation can alter Gene Expression and is a Therapeutic Target in Cancer. *Cancer Cell* 26, 577–590. <https://doi.org/10.1016/j.ccr.2014.07.028>
- Zhang, Q., Raoof, M., Chen, Y., Sumi, Y., Sursal, T., Junger, W., Brohi, K., Itagaki, K., Hauser, C.J., 2010. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464, 104.